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Chromosomal Methods in Population Studies

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A brief description of chromosome aberrations and sister chromatid exchange (SCE) as cytogenetic endpoints for evaluation of DNA damaging agents is presented. Problems associated with the use of cytogenetic assays as population monitors of radiation and chemical exposures are discussed. Adequate cell sample size requirements and accurate assessment of cummulative exposure effects with increasing age are stressed as important considerations for reliable cost-benefit analysis of population studies involving low level exposures.

Examples of population studies using SCE as an indicator of specific chemical exposures are cited, and factors contributing to variations in control baseline SCE levels are discussed. Possible implications of population cytogenetic data on general public health are suggested.

Over the past 20 years, "conventional" chromosome aberration scoring in human peripheral blood lymphocytes has been extensively used as a monitor for radiation and chemical induced cytogenetic toxicity. More recently, the introduction of banding as well as sister chromatid exchange (SCE) techniques has provided improved accuracy and sensitivity in detection of DNA damaging agents.

At the microscopic level, cytogenetic effects might be evident as aneuploidy (alterations in chromosome numbers) or as aberrations (alterations in chromosome morphology). At the molecular level, DNA damage may be characterized by disruption of the integrity of the phosphoribose backbone via direct single- or double-strand breakage as typically resulting from radiation or, alternatively, by modification of the purine or pyrimidine bases. Although the latter may produce labile ribosyl bonds, DNA strand breakage does not necessarily occur. Nevertheless, the various types of DNA damage elicit repair processes whose effects can become apparent as morphologically altered chromosomes. The specific chromosomal consequence of DNA damage is a function of the type of DNA lesion, cell cycle time of induction of lesion, and its persistence (Fig. 1). DNA damage initiated prior to DNA synthesis (S) may undergo interchromosomal or intrachromosomal repair processes and, following replication during S, produce some chromosome-type aberrations as dicentrics, acentrics, fragments, terminal or interstitial deletions and breaks. Lesions induced during or persisting until S may initiate chromatid-type aberrations or increased SCE frequencies. Abnormal morphological changes are evidence of lack of repair or misrepair and, as such, are potentially lethal. On the other hand, SCE is visible evidence of successful repair, a condition expected to be more compatible with events dependent upon cell survival (e.g. mutagenesis and carcinogenesis). Some fundamentally different cellular lesions or processes may produce only aberrations or SCE whereas other lesions may, under appropriate conditions, induce both SCE and aberrations, with SCE being more sensitive at lower agent concentration (*1*).

The use of cytogenetic aberration scoring of human blood cells has proved to be a sensitive means of detecting biological changes produced by radiation exposures of smaller magnitude than can be detected by any other practical test system. It has made possible studies involving short-term external radiation exposure *in vivo* from a variety of radiation sources, as well as parallel *in vitro* studies. They have led to enhanced understanding of basic radiobiological mechanisms as well as an

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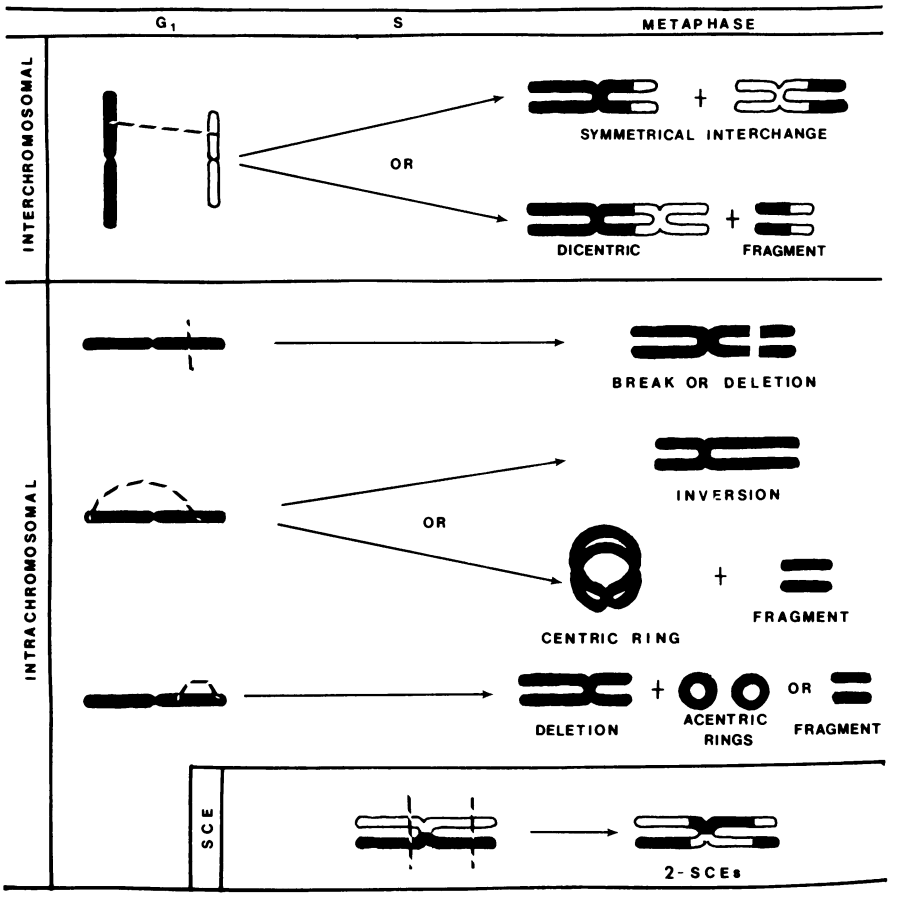

FIGURE 1. Formation of chromosome type aberrations and SCE.

application of "biologic dosimetry" which has been helpful in the management of accidental human over-exposure patients, as well as those patients receiving radionuclide therapy (*2*). When applied in accidentally exposed radiation workers, Lloyd et al. (*3*) found a lower limit of dose estimate, with 500 cells analyzed, at 4 rad for 250 kV x-rays and 20 rad for cobalt-60 gamma radiation.

Only a relatively few investigations (*4-9*), presented in Table 1, have been concerned with the *in vivo* response of human lymphocyte chromosomes to lower levels of external and/or internal radiation exposure received on a continuous or intermittent basis over long time periods despite the uncertainties about and interest in such population exposures. In general, these studies are difficult to carry out because of the complexities of accurate radiation exposure assessment at near background environmental levels and the large number of cells which must be evaluated in order to delineate any significant departures from the normal range of aberrations. Note the variations in the units used in quantitating the radiation exposures, which make it difficult to summate the results. In general, the studies give some support to the idea that radiation-induced chromosome aberrations can be detected in populations in which sufficient numbers of cells are scored following radiation exposure at levels beginning at low multiples of the natural environmental radiation background.

Because of the large number of cells which require scoring for detection of such low levels effects, these changes are not detectable in individuals in whom the usual diagnostic level of cells are scored. In our cytogenetics laboratory, the preparation, scoring and analysis of 200 mitotic cells takes approximately 14 man-hours. It is therefore evident that a careful investigation of the feasibility of cytogenetic screening for epidemiologic investigations is necessary to make a meaningful cost/benefit judgement about the proposed research. A recent approach to the sample size problem has been reported by Whorton and colleagues (*10*). They studied the magnitude of

Table 1. *In vivo* cytogenetic studies of low-level radiated population.

Exposure source	Dose groups	Cells/dose group[a]	Reference
Environmental uranium and thorium	640 mr/yr	C = 9,000 X = 13,242	Barcinski et al. (*14*)
Environmental radon-222	100–1200 mrad/in 6 mo.	X = 30,598 Total (? avg–3800/grp)	Pohl-Ruhling et al. (*5*)
Environmental radon-222, drinking water	3–1200 nCi/L	C = 4,520 X = 1,000–2,000	Stenstrand et al. (*6*)
Diagnostic urography	1–4r	C = 1,687 X = 1,627	Kucerova et al. (*7*)
Uranium workers	< 100 to > 3,000 WLM	C = 1,950 X = 500–2,500	Brandon et al. (*8*)
Nuclear shipyard workers	0.2–33 rem	C = 1,500 X = 600–9,000	Evans et al. (*9*)

[a]C = control; X = exposed.

variation in the proportion of abnormal cells and estimated the number of subjects and the number of cells per subject needed to detect significant increases of predetermined size over a control value with a type I error of $\alpha = 0.05$ and type II errors of $\beta = 0.20$ or 0.10. They found that with $\alpha = 0.05$ and $\beta = 0.10$, about 20 subjects per group and 200 cells per subject were needed to detect a doubling over a control value for the variable occurring at a rate of 0.02.

In another study of this problem, Redmond and Gur (*11*) found that when the average radiation exposure was set at 100 mrem and detection of a statistically significant increase in dicentric frequency was desired with a power of 0.75 ($\alpha = 0.05$) assuming the relationship of age to chromosomal sensitivity for radiation-induced dicentric formation is that described by Evans, et al. (*9*), the following number of cells would have to be scored: for a group at age 25, 10.6×10^6; for age 40, 2.5×10^6; for age 55, 1.1×10^6. With background radiation-induced aberration frequencies assumed to be dose-dependent, these requirements would change slightly to 9.7×10^6, 2.3×10^6 and 1.0×10^6. They also found that if 20,000 cells are to be scored for dicentric frequency and the required power is 0.75 ($\alpha = 0.05$), with a dicentric background frequency of $2.5 \pm 1 \times 10^{-4}$ per cell and age-related background radiation sensitivity for radiation-induced dicentric formation were present, then for a group at 25, with a dicentric sensitivity of 1.6 ± 0.6 per 10^4 person-rem, the lowest dose detectable would be 4.1 rem; for age 40, with a dicentric formation sensitivity of 3.3 ± 0.6 per 10^4 person rem, the lowest detectable exposure would be 2.0 rem; and for age 55, with a dicentric sensitivity of 5.0 ± 1.0 per 10^4 person-rem, the lowest detectable exposure would be 1.3 rem. These observations are considered in more detail in Dr. Redmond's presentation (*11*).

It becomes apparent from the foregoing that the use of cytogenetic techniques in epidemiologic populations exposed to low doses of radiation over long time periods must consider the sample size as well as the effect of age on the end point. The non-specific effect of age on increasing aneupolidy was described in some detail by Court-Brown (*12*) in his classic monograph on human population cytogenetics. The relationship of increasing age to cytogenetic radiosensitivity was reviewed by Evans, et al. (*9*) recently. Both studies underscore the need to control carefully for age effects in cytogenetic population studies. In addition, in some low-dose radiation studies, it is evident that cumulative natural radiation background exposure and medical diagnostic radiation exposure, both age-related, could be comparable in magnitude to the environmental exposure being assessed. This possibility must be taken into account in designing and analyzing such population studies. Other considerations include those of other agents which may damage chromosomes such as chemicals and virus infections.

The utilization of cytogenetic studies to detect chemical damage to chromosomes is of relatively recent origin. Initially, *in vitro* studies as well as animal and exposure experiments served as the basis for information about such cytogenetic damage, as reviewed in detail by Shaw (*13*) in 1970. More recently there have been attempts to extend the utilization of this technique to human *in vivo* exposed populations. Two series of studies summarized by Forni et al. (*14*) and by Tough et al. (*15*) are related to benzene-exposed workers in Italy and Great Britain. While it was evident that high exposures can produce chromosome damage, no significant increases in the level of chromosome abnormalities were found in some of the studies involving workers exposed to low levels. An increase in sensitivity to such damage with increas-

ing age was also demonstrated by Tough et al. (*15*). Other areas in which chemical effects have been detected have involved cancer chemotherapeutic agents, and consciousness altering drugs. More recently occupational exposures have come under study including those to vinyl chloride, arsenic, lead and others. These are well summarized in a recent review by Purchase (*16*).

Among the difficulties in interpreting the occupational exposure studies, beyond those already indicated as confounding factors in general population studies, are the problems of quantitation of duration of exposure and dose rate especially in situations where there may be intermittent peaks of brief over-exposure. Also the time after an exposure which has elapsed before the chromosome study is performed has a great effect on the dose-response relationship. In general, it appears that population surveillance by chromosome aberration scoring may be useful in chemically exposed groups if sufficient quantitative exposure information is available and large enough cell sample size studies are performed. Such surveillance may be facilitated by the automation of aberration scoring, which appears to be feasible in studies performed at this institution (*17*).

The recent development of SCE techniques has provided a more sensitive means for evaluation of cytogenetic effects (*18, 19*) of a wide variety of environmental, industrial and chemotherapeutic agents. Sister chromatid differentiation of human lymphocytes can be accomplished by incorporating the thymidine analog, 5-bromo-2′-deoxyuridine (BrdU) into chromosomal DNA for the duration of two replication cycles. The chromosomes can subsequently be stained differentially with fluorescent or Giemsa stain (*18*). SCE are recognized as reciprocal exchanges of differentially stained regions between sister chromatids. The frequency of such exchanges may increase following exposure to various agents.

Because the use of SCE as a population monitoring method is relatively recent, many current studies are concerned with establishment of control baselines and identification of factors contributing to variation in baselines. A summary of baseline values as determined in normal control subjects (> 10 individuals/study and approximately 20 cells/individual) in various laboratories (*20-33*) is illustrated in Figure 2. Possible factors contributing to the observed variation between laboratories might be due to: real differences in methods of culturing and/or scoring cells or real differences in the populations studied.

With respect to culturing methods, although BrdU concentration in the culture media may play some role in SCE induction (*18*), all studied cited employed concentrations between 1 and 160 μM, a range over which minimal effects on SCE variance were reported (*26*). Nevertheless, establishment of standard culturing and scoring procedures might eventually reduce interlaboratory variations.

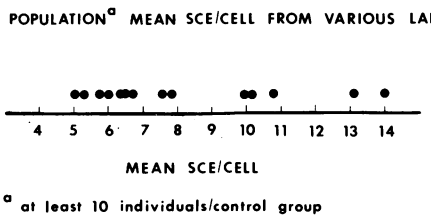

FIGURE 2. Variance of control SCE/cell among various laboratories.

With regard to population differences many factors have been evaluated. Variation within control subjects, examined by comparison of duplicate cultures (*23, 31*) or of repeat cultures from the same individual taken at 3 month intervals (*31*) revealed no significant differences. Likewise, no significant differences were apparent between sexes (*20, 31, 34*) or with age from 0 to 85 yr (*26, 31*).

The most extensive evaluation of a control population was reported by Morgan and Crossen (*31*). In their study which included 1000 cells from a total of 50 individuals, the population mean SCE/cell was 7.9 ± 1.36. Within subjects the range of SCE/cell was 1-21 with a mean variance of 2.9. The distribution was judged normal by the nonparametric Kolmogorov-Smirnov test. However, a normal distribution is rejected if the data is tested with the more powerful Shapiro-Wilkes test for normality. Examination of the distribution reveals an apparent skewing with possible outlying values. The most extreme outlier (outside the 99.7% range) reportedly was an individual who was engaged as a worker in the rubber industry, an occupation long associated with an increased incidence of malignancy. For all other control individuals, no indication was made concerning smoking habits and/or general health, factors which are critical to SCE baseline levels.

Significantly elevated SCE/cell means as well as wider ranges of SCE/cell were observed in smokers relative to nonsmokers (*28, 32*). Although the number of cigarettes smoked per day and years duration of smoking both contributed to elevated SCE frequencies, the highest frequencies were demonstrated by individuals who smoked more than 10 cigarettes per day irrespective of duration.

Increased SCE levels were also exhibited by patients treated with chemotherapeutic agents (*35*). Such increases are instructive, in that acute

doses generally produce transient effects whereas repeated administration of smaller lower doses result in sustained increases, persisting for periods of three months or more. These results reflect the relatively long-lived nature of SCE-inducing lesions and lymphocyte life-span *in vivo* relative to the expectedly much shorter plasmatic half-life of active drug metabolites.

Significant increases in SCE frequencies (1.5-2 × baseline) have also been observed in lymphocytes of individuals with viral diseases such as herpes simplex, cold/flu and hepatitis (*27*); arsenic-induced skin cancers (*20*); and newly diagnosed acute lymphoblastic leukemia (*33*).

In an epidemiologic occupational study (*25*), SCE and chromosome aberrations were examined in lymphocytes of workers exposed to various organic solvents and of children (0-11 years) of mothers who were pregnant at the time of exposure. One group of technicians as well as the exposed children had significantly higher mean SCE/cell and chromosome aberrations relative to corresponding nonexposed controls but no correlation between SCE frequencies and aberrations was apparent. The increased effects in children of exposed mothers suggest that active agents might be able to pass through the placenta and produce lesions in lymphocytes which may remain latent for years. However, contrary to other studies (*26*, *31*) adult controls had higher mean SCE frequencies that did control children. Detailed interviews revealed that many control adults previously had diagnostic x-rays, had taken different drugs for a variety of disorders, and were smokers. Hence the age difference might be due to continuous exposures more common to the adult environment. Two other studies indicate that SCE may be a useful tool in occupation studies. In a recent report regarding SCE levels in petroleum refinery workers by Carrano et al. (*36*), approximately half of 22 workers had SCE frequencies in excess of two standard errors above the "nonexposed" group mean. While vinyl chloride workers exposed to very low doses of 0.1 ppm for the relatively short period of two years demonstrated normal SCE and aberration levels (*37*) both were elevated in workers exposed to 20 ppm and higher for 10 or more years (*38*). Thus, induced chromosomal changes apparently depends upon dose and length of exposure.

It is clear from these population SCE studies that there are many factors unrelated to specific population exposures which might confound control as well as exposure results. Such factors must be identified and as far as possible incorporated into the experimental design. It might be expected that chronic low level effects may not produce dramatic increases in population means, in which case nonparametric statistics might be more appropriate for comparison of control and exposed groups. For example, careful examination of frequency distributions may reveal a greater than expected proportion of exposed individuals having slightly elevated SCE frequencies.

Since not all chemical and physical agents (notably radiation) are effective SCE inducers, evidence regarding specific activities should be sought by *in vitro* laboratory testing or *in vivo* animal models before employing the assay in large scale population studies involving known agents.

Regardless of the specific chromosomal endpoint employed, question arises as to interpretation of population cytogenetic data. It must be kept in mind that false negatives inherently result due to limitations in the sensitivities of particular assays. Although SCE is generally more sensitive than chromosome aberrations, SCE are not induced by all mutagens and carcinogens. On the other hand, chromosome aberrations are induced by a wider range of agents but represent rather gross, potentially lethal genetic alterations and require higher concentrations to produce significant effects. Furthermore, the lymphocyte test system employed for either assay is characterized by a G_0 cell population which may be more resistant than other more proliferative critical body tissues and, in addition, possesses repair capability which may diminish the apparent effect if prolonged time intervenes before assay.

On the other hand, there is concern regarding the implications of elevated chromosome aberrations or SCE on an individual's or on the general public's genetic health. Man-made relaxation of genetic selection due to improved general medical care over the past 50 years, coupled with increasing environmental exposures, might be expected to produce even greater increases in human genetic diseases in future generations. Yet, the extent to which mutation in lymphocytes can be translated into germ cell effects and hence heritable effects remain to be determined.

Perhaps of more immediate concern to present populations are the facts that many carcinogenic agents have been demonstrated to be mutagenic (*39*) and many mutagens/carcinogens produce chromosome aberrations or increase SCE in cultured lymphocytes. However, although hypothetical relationships exist between chromosome aberrations and the origin of tumors (*40*), chromosomal effects are not necessarily the causative factor in carcinogenesis.

In spite of the facts that lymphocyte cytogenetic

test systems detect only some of a wide spectrum of genetic effects and the ultimate consequences to individuals and populations cannot, at present, be explicitly defined, such test systems are uniquely accessible human test systems which provide evidence of cytogenetic damage and under appropriate exposure conditions, are an index for estimation of human risk.

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